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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/720,411	03/12/2001	Jan Tadeusz Czernuszka	480821.90043	1013

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EXAMINER

KISHORE, GOLLAMUDI S

ART UNIT

PAPER NUMBER

1615

DATE MAILED: 05/07/2003

12

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.
09/720,411

Applicant(s)
Czernusza

Examiner
Gollamudi Kishore

Art Unit
1615



-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE three MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on Feb 12, 2003
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1, 2, 6-16, 18-23, 25-30, and 34-36 is/are pending in the application.
- 4a) Of the above, claim(s) 18-20 and 25 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 2, 6-16, 21-23, 26-30, and 34-36 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____ 6) ☐ Other:

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DETAILED ACTION

The request for the extension of time and amendment filed on 2-12-03 are acknowledged.

Claims included in the prosecution are 1-2, 6-16, 18-23, 26-30 and 34-36.

Claim Rejections - 35 USC § 112

- 1. The following is a quotation of the second paragraph of 35 U.S.C. 112:**

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

- 2. Claims 14-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.**

The vesicles in claim 1 are coated with a layer of calcium phosphate; this means the pharmaceutically active agent is encapsulated. If so, it is unclear as to how the encapsulated agent can assist the binding of the vesicle whose surface is covered with calcium phosphate to the bone as recited in claim 14. Applicant argues that the claim has been amended and thus resolves this issue. It is unclear as to how it resolves the issue since the amended claim still recites, "wherein the pharmaceutically active compound assists the binding to bone". This amendment is actually is more confusing since it makes it unclear as to what is binding to bone and the original issue raised by the examiner still remains unresolved.

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Claim Rejections - 35 USC § 102

3. **The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:**

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. **Claims 1-2, 6, 10, 16, 21-23 and 34 are rejected under 35 U.S.C. 102(b) as being anticipated by Eanes (Bone and Mineral, 17, pp., 269-272, 1992 of record or Eanes (Calcif. Tissue Int (40, pp 43-48, 1987)**

Eanes in both publications discloses liposomes coated with calcium phosphate; liposomes are made of phosphatidylcholine . The liposomes are suspended in NaCl and therefore, the surface layer containing chloride ions as recited in claim 6 is inherent in the prior art composition (note the abstract, and Table 1 on page 270 in Bone and Mineral; summary, Materials and Methods and discussion in Calcif. Tissue Int).

Applicant's arguments have been fully considered, but are not found to be persuasive. The reference meets the requirements of instant amended claims for the following reasons. A liposome is a bilayer structure containing two layers of phospholipids; in each layer, the hydrophilic moiety of the phospholipid is oriented toward the aqueous compartments, namely, the inner cavity and the external medium. Since calcium phosphate is not lipophilic, it would be present in the aqueous interior and in the lipid bilayer itself.

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Therefore, the reference which teaches vesicles in which the aqueous interior contains calcium phosphate and not in the inner layer meets the requirements of instant claims. Claim 34 which recites 'consists essentially of' is included in this rejection on the same basis.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

6. Claims 7-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eanes in Bone and Mineral or Calcif. Tissue Int., cited above.

As pointed out above, Eanes in both publications discloses liposomes coated with calcium phosphate; liposomes are made of phosphatidylcholine . The liposomes are suspended in NaCl and therefore, the surface layer containing chloride ions as recited in claim 6 is inherent in the prior art composition (note the abstract, and Table 1 on page 270). What is lacking in Eanes is the explicit teaching of the thickness of the coating of the vesicles by the calcium phosphate. However, on page 270, Eanes appear to suggest that the coating on the external surface is time dependent and PL dependent and therefore, it

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would have been obvious to one of ordinary skill in the art to obtain the vesicles with a desired coating thickness by varying the time and the selection of suitable phospholipids.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that instant liposomes are fundamentally different from Eanes. This argument is not found to be persuasive since the differences are not reflected in the claims. Applicant argues that thickness is not important to Eanes investigations. This argument is not found to be persuasive since whether it is important or not, the location pointed out above, is suggestive to one of ordinary skill in the art that one can change the thickness by varying the times and the amount of PL if desired.

7. Claims 1-2, 6-16, 21-23, 26-29 and 34-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over EP 0 479 582 of record in combination with either of Eanes (Bone and Mineral) or Calcif. Tissue Int., cited above and Chung (5,039,546).

EP discloses multilamellar liposomes containing an antibiotic. The liposomes are suspended in hydroxyapatite (hydroxy -calcium phosphate). The compositions are useful as dental implants (note the abstract, columns 4-7 and claims). What is lacking in EP is the teaching of the coating of the liposomes with apatite (calcium phosphate) instead of hydroxy-apatite. What is also lacking in EP is the teachings of the attachment of the liposomes to a surface.

Eanes as discussed above teaches the formation of coatings of calcium phosphate on the liposomal surface when suspended in calcium phosphate solutions.

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Chung discloses that for dental implants (ceramic or metal) coated with either hydroxyapatite or calcium phosphate are known and routinely used in dental and orthopaedic areas (note the abstract, columns 1-2 and claims).

The use of calcium phosphate instead of hydroxyapatite in EP would have been obvious to one of ordinary skill in the art since Eanes teaches that the liposomes can be coated with calcium phosphate and Chung teaches that both hydroxyapatite and calcium phosphates are routinely used in dental implant area. Further coating the composition of EP over a substrate would have been obvious to one of ordinary skill in the art, with a reasonable expectation of success since Chung teaches that either hydroxyapatite or apatite are coated on a substrate for use in dental and orthopaedic areas. Chung does not disclose specifically the sizes of the implants. However, it is deemed to be within the skill of the art to use the desired sizes since sizes depend on the site the implant is to be used.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that EP is concerned with drug delivery whereas Eanes is concerned with the way in which calcium phosphate is formed on liposomes. This argument is not found to be persuasive. As clearly evident from EP, its teachings are not just for the drug delivery, but for the generation of new bone tissue (note the abstract). With regard to Eanes, the author clearly states in the introductory sections in both publications, that the system studied is an in vitro model for the extracellular calcification in many skeletal tissues. Eanes further states that the phospholipid, phosphatidylserine

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(PS) is implicated in the calcification of a number of tissue structures and that this lipid is enriched at the sites of initial mineralization in these tissues, especially where matrix vesicles are most abundant. Eanes also teaches that PS also has a ready affinity for calcium ions which, in the presence of P 1, can result in calcifiable complexes in dilute aqueous solutions (see for e.g., col. 2 on page 43 and col. 1 on page 44). Therefore, combining these references is proper.

Applicant argues that Chung is concerned with increasing the stability of hydroxyapatite or calcium phosphate coatings on metal implants and that it is not concerned with liposomes. This argument is not found to be persuasive since Chung is combined for the teachings of the use of either calcium phosphate compounds for implants just as in instant invention. Applicant's arguments that hydroxyapatite is preferred in Chung are not found to be persuasive since Chung teaches the art known use of both and choosing one of the prior art's compounds and finding that it works too does not show unexpected nature of the results.

8. Claims 30 is rejected under 35 U.S.C. 103(a) as being unpatentable over EP 0 479 582 of record in combination with either of Eanes (Bone and Mineral) or Calcif. Tissue Int., cited above and Chung (5,039,546), further in view of Redepinning (5,310,464).

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The teachings of EP, Eanes and Chung have been discussed above. Chung in particular teaches the coating of calcium phosphate on metal or ceramic implants. What is lacking in the cited prior art is that the process of coating be conducted electrolytically.

Redepenning discloses that when the metallic implants are coated by electrolytic process, the coating is superior to the coating obtained by conventional processes.

Redepenning's process involves immersing the implant in a solution of calcium and dihydrogen phosphate and coating the implant by electrolysis (note the abstract, col. 3, line 38 et seq.;, and claims).

The use of electrolysis for the coating of liposomes containing an outer layer of calcium phosphate over a metallic implant would have been obvious to one of ordinary skill in the art because Redepenning teaches that electrolytic process is superior to the conventional processes.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant while admitting that Redepenning discloses an electrolytic deposition, argue that he uses a different calcium phosphate and there is no reason why one with skill in the art would adopt a similar electrodeposition process for depositing vesicles possessing a preformed calcium layer on their surface. This argument is not found to be persuasive since both are calcium phosphate compounds and therefore, one of ordinary skill in the art would be able to use instant calcium phosphate in the deposition process with a reasonable expectation of success. Besides, instant claim 30 does not recite the

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condition, that is, the vesicles already possess a preformed calcium layer on their surface.

The examiner notes that electrodeposition is practiced in many arts (gold plating objects for example) since the process gives an uniform deposition of the coating substance.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

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10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *G.S. Kishore* whose telephone number is (703) 308-2440.

The examiner can normally be reached on Monday-Thursday from 6:30 A.M. to 4:00 P.M. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, T.K. Page, can be reached on (703)308-2927. The fax phone number for this Group is (703)305-3592.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [thurman.page@uspto.gov].

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

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Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703)308-1235.



Gollamudi S. Kishore, Ph. D

Primary Examiner

Group 1600

gsk

May 6, 2003